Article

Comprehensive Meta-Analysis of Excess Mortality in Depression in the General Community Versus Patients With Specific Illnesses

Pim Cuijpers, Ph.D.

Nicole Vogelzangs, Ph.D.

Jos Twisk, Ph.D.

Annet Kleiboer, Ph.D.

Juan Li, Ph.D.

Brenda W. Penninx, Ph.D.

Objective: Several hundred studies have shown that depression is associated with an elevated risk of dying at follow-up. It is not clear, however, whether the mechanisms for this association are disease specific, leading to higher mortality in specific patient groups, or generic, resulting in comparable mortality rates in all patient groups as well as in community samples. The authors conducted a comprehensive meta-analysis of prospective studies of community as well as patient samples associating depression at baseline with excess mortality at follow-up.

Method: The authors conducted systematic searches of PubMed, PsycINFO, and Embase. Studies were included if depression was measured with a standardized instrument and mortality was reported for both depressed and nondepressed participants at follow-up.

Results: A total of 293 studies including 1,813,733 participants (135,007 depressed and 1,678,726 nondepressed) from 35 countries were included. The overall unadjusted relative risk of mortality in depressed relative to nondepressed participants was 1.64 (95% CI=1.56–1.76), with high heterogeneity (I^2=83, 95% CI=80–84). After adjustment for publication bias, the overall relative risk was reduced to 1.52 (95% CI=1.45–1.59). No strong indications were found that the pooled relative risk was different across the relatively healthy community samples and specific patient samples with heart disease, cancer, kidney disease, or other disease, except for a significantly higher risk in patients with chronic obstructive pulmonary disease ($p<0.05$). Also, the relative risk was lower when the follow-up period was longer and when the quality of the study was higher.

Conclusions: The authors could confirm the presence of a significant association between depression and excess mortality, although this association may have been overestimated because of publication bias and low study quality. Few indications were found that this association is stronger in community or specific patient samples.

Am J Psychiatry Cuijpers et al.; AiA:1–10

After more than 150 years of studies examining the association between mental disorders and excess mortality (1, 2), it is well established that mortality rates are significantly elevated in depressed patients. A significant association between depression and excess mortality has been confirmed in several hundred studies in many different populations, including community samples (3) and patients with heart disease (4), cancer (5), stroke (6), and diabetes (7).

Although no single comprehensive model has yet described the causal mechanisms linking depression to excess mortality, several key mechanisms have been proposed. Some of these are more or less disease specific. In cancer research, for example, it has been suggested that depression-related stress may have a negative effect on the cellular processes involved in the repair of damaged DNA (8) and may accelerate tumor cell growth and promote tumor migration and invasive capacity (9), which subsequently results in poorer cancer outcomes (10). In heart disease research, it has been hypothesized that the excess mortality in depression is associated with factors such as vascular endothelial dysfunction (11), a prolonged QT interval (12), lower heart rate variability reflecting altered cardiac autonomic tone (13), and increased platelet aggregation (11). In addition, in patients with somatic diseases, depression could have an unfavorable impact on adherence to a prescribed treatment regimen (14), in turn having a direct impact on survival.

On the other hand, several of the mechanisms that have been proposed to mediate the association between depression and mortality are not specific to one disease and may lead to different diseases and multiple pathways to death. For example, there is evidence suggesting that dysregulation of central biological stress systems, including hypothalamic-pituitary-adrenal axis hyperactivity (15), neuroimmune dysregulations (16), and sympathoadrenergic dysregulation, may have a causal role in the association between depression and overall mortality (3). Furthermore, rates of negative lifestyle factors, such as physical inactivity, smoking, alcohol consumption, and

unhealthy eating patterns (14), are higher in depressed patients and may explain part of the association between depression and mortality, independent of whether an individual already has a somatic disease.

If excess mortality in depression is caused by disease-specific mechanisms, it can be expected that mortality risks associated with depression would be higher in depressed patients than in other patients or community samples. However, if the excess mortality is more related to generic factors that are not specific to one disease, we would expect a comparable association between depression and mortality in any patient or community sample.

To the best of our knowledge, no meta-analytic research has yet examined whether or not excess mortality in depression is higher in specific patient groups. Meta-analyses are an excellent method for examining this research question because they can integrate the results of multiple studies and thereby provide a better estimate of the true mortality risk of depression across different types of populations. We conducted a comprehensive meta-analysis of prospective studies examining the association between depression at baseline and mortality at follow-up. We included specific patient populations as well as the much healthier community-based samples and any other study in which the association between depression at baseline and mortality at follow-up was examined.

Method

Selection of Studies

Studies were identified by several methods. First, we conducted comprehensive literature searches (up to April 2013) in three bibliographical databases—PubMed, PsycINFO, and Embase—combining terms indicating depression (such as major depression, mood disorder, depression, depressive), mortality (death, survival), and prospective design (incidence, follow-up studies, longitudinal studies, prospective studies). Both text terms and keywords were used. The detailed search string for our PubMed search is provided in Appendix A in the data supplement that accompanies the online edition of this article. We also examined the references of included studies, as well as the references of earlier meta-analyses examining the association between depression and mortality (see Appendix B in the data supplement). We retrieved the full-text papers of studies that possibly met our inclusion criteria. Full-text papers were examined by two independent raters for possible inclusion. Disagreements were resolved by discussion.

We included studies with a prospective design in which depression was examined at baseline and all-cause mortality was reported at follow-up. Depression had to be assessed with a standardized depression measure (either a diagnostic interview or a self-report questionnaire). We included studies in any target group (community, patient, and any other sample) as well as case-control studies. Studies were excluded if insufficient data were presented to calculate mortality rates at follow-up in the depressed and nondepressed groups. We excluded studies in which the instrument for assessing depression was not standardized (e.g., studies relying on self-report of antidepressant use to assess depression, those using nonstandardized interviews, and those using only one question), studies based on trials examining the effects of an intervention, and studies in children and adolescents.

Data Extraction and Quality Assessment

We assessed the validity of studies with a quality rating scale based on the instrument developed by Hayden et al. (17). We adapted the specific items but retained five of the six basic areas of potential bias: study participation (the study sample represents the population of interest on key characteristics), study attrition, adequate outcome measurement, adequate measurement of confounding variables, and adequate statistical analysis. The sixth area of potential bias (the prognostic factor of interest is adequately measured) was not used because an adequate measure of depression was used as an inclusion criterion for this study. The instrument is presented in Appendix C in the online data supplement, and the ratings for included studies are presented in Appendix D. Ratings were conducted by two independent researchers, and disagreements were resolved by discussion. Agreement between raters after the first ratings was good for four of the five areas (kappa values for attrition, outcome measurement, measurement of confounders, and statistical analysis ranged from 0.69 to 0.78) but was moderate (0.56) for study participation (18).

To assess excess mortality in different community and patient groups, we first categorized the studies into community samples and various patient samples by disease. We also rated several other characteristics of the included studies: definition of depression (depression according to a self-report measure or a diagnostic interview), prevalence of depression, follow-up period, type of outcome measure (hazard ratio, relative risk, odds ratio, or exact numbers of deaths in depressed and nondepressed participants), and country/continent where the study was conducted.

Meta-Analyses

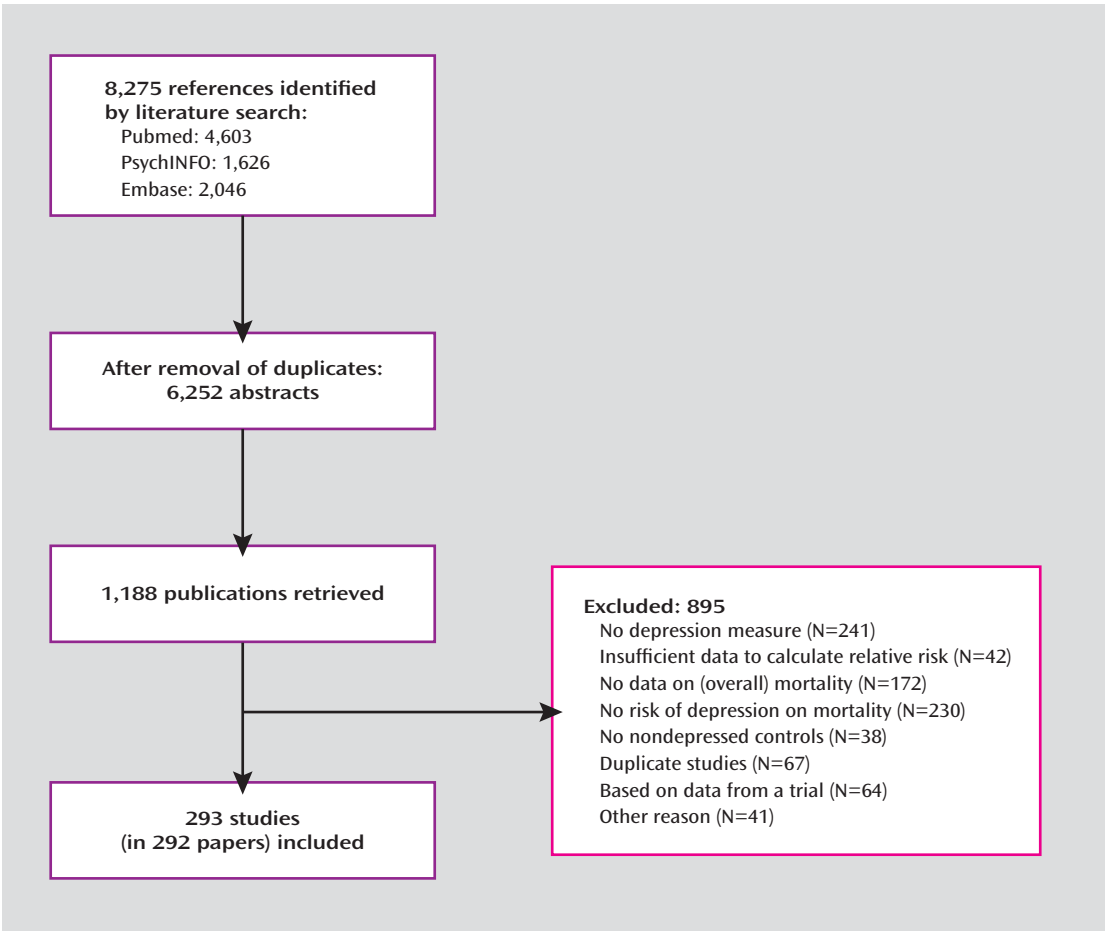
The included studies used different outcome measures to characterize the association between depression and mortality. Some reported the exact number of deaths in the depressed and nondepressed groups, while others reported the hazard ratio, the relative risk, or the odds ratio. We used the relative risk as the main outcome measure (hazard ratio can be considered to be a specific type of relative risk adjusted for time to death; the odds ratio approximates the relative risk when the outcome, in our case mortality, is 10% or lower, which was the case in most studies; relative risk was calculated directly when the exact numbers of deaths per group were reported). In sensitivity analyses, we examined whether the pooled relative risks differed for each of these four types of outcome statistics.

To calculate pooled relative risks, we used the computer program Comprehensive Meta-Analysis, version 2.2.021 (www.meta-analysis.com). Because we expected considerable heterogeneity among the studies, we calculated the pooled relative risk using a random-effects model.

To examine heterogeneity, we calculated the I^2 statistic. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity, with 25% considered low, 50% moderate, and 75% high heterogeneity (19). We calculated 95% confidence intervals around I^2 (2, 20) using the noncentral chi-square-based approach within the heterogi module for Stata (21). We tested for significant heterogeneity with the Q statistic.

Subgroup analyses were conducted according to the mixed-effects model (22), in which studies within subgroups are pooled with the random-effects model while tests for significant differences between subgroups are conducted with the fixed-effects model. Bivariate meta-regression analyses were conducted according to the procedures implemented in Comprehensive

FIGURE 1. Flowchart of Inclusion of Studies in a Meta-Analysis of Excess Mortality in Depression in Community and Patient Studies



Meta-Analysis. Multivariate meta-regression analyses were conducted in Stata, version 11.0 (StataCorp, College Station, Tex.).

Possible publication bias was tested by inspecting the funnel plot and by Duval and Tweedie's trim-and-fill procedure (23), which yields an estimate of the effect size after the publication bias has been taken into account. We also conducted Egger's test of the intercept to quantify the bias captured by the funnel plot and tested whether it was significant.

Results

Selection of Studies

Figure 1 summarizes the study selection process. After examining a total of 8,275 abstracts (6,252 after removal of duplicates), we retrieved 1,188 full-text articles for further consideration. We excluded 895 of the retrieved articles (reasons for exclusion are provided in Figure 1). A total of 293 studies met inclusion criteria. Characteristics of the individual studies are provided in Appendix D in the online data supplement (references are listed in Appendix E).

Characteristics of Included Studies

The 293 studies included a total of 1,813,733 respondents, of whom 135,007 were depressed and 1,678,726 were not depressed (in studies with missing prevalence rates, we imputed these values with the pooled prevalence rates of all other studies). Selected characteristics of the 293 studies are presented in Table 1.

The studies were conducted in 35 countries from all populated continents, although most studies were conducted in the United States (N=114) and Europe (N=115). Most studies were conducted in samples recruited from the general population (N=104), heart disease patients (N=69), cancer patients (N=29), and other patient populations (N=84). Depression was established by diagnostic interview in 82 studies and by a self-report measure in 211 studies. Follow-up periods varied widely; we categorized them as <1 year (N=56), 1–5 years (N=125), 6–10 years (N=84), and >10 years (N=38). Most studies were conducted after the year 2000 (N=216). All case-control studies were nested case-control studies.

The quality of the included studies varied (see Appendix D in the online data supplement). In the domain of study participation, 164 studies (56%) scored positive; 186 studies (64%) scored positive on study attrition, 201 (69%) on outcome measurement, 121 (41%) on confounding

TABLE 1. Selected Characteristics of Studies Examining the Association Between Depression and Excess Mortality

	Studies		Respondents	
Characteristic	N	%	N	%
All studies	293	100.0	1,813,733	100.0
Group				
Community samples	104	35.5	1,685,141	92.1
Heart disease patients	69	23.5	43,749	2.4
Cancer patients	29	9.9	10,817	0.6
Kidney disease patients	16	5.5	12,003	0.7
Diabetes patients	8	2.7	28,382	1.6
Chronic obstructive pulmonary disease patients	7	2.4	1,267	0.1
HIV patients	5	1.7	5,637	0.3
Stroke patients	5	1.7	2,380	0.1
Dementia/cognitive decline patients	4	1.4	1,091	0.1
Hip fracture/surgery patients	4	1.4	1,542	0.1
Mixed patient groups[a]	18	6.1	7,717	0.4
Other patient groups[b]	8	2.7	7,652	0.4
Nursing home residents	9	3.1	4,678	0.3
Case-control studies	7	2.4	1,677	0.1
Definition of depression				
Diagnostic interview	82	28.0	1,130,932	62.4
Self-report measure	211	72.0	682,801	37.6
Follow-up period				
≤1 year	56	19.1	42,307	2.3
1–2 years	41	14.0	43,254	2.4
3–5 years	84	28.7	254,941	14.1
5–10 years	71	24.2	279,258	15.4
>10 years	38	13.0	1,193,130	65.8
Not reported	3	1.0	843	0.0
Prevalence of depression				
<10%	38	13.0	1,241,520	68.5
10%–19%	77	26.3	263,432	14.5
20%–29%	71	24.2	208,806	11.5
30%–40%	40	13.7	23,467	1.3
>40%	44	15.0	22,713	1.3
Not reported	23	7.8	53,795	3.0
Country				
United States	114	38.9	430,623	23.7
European countries	115	39.2	1321174	72.8
Other Western countries	26	8.9	36,494	2.0
East Asian countries	25	8.5	18673	1.0
Other countries	13	4.4	6,769	0.4
Publication year				
<1990	16	5.5	13,418	0.7
1991–1995	18	6.1	30,296	1.6
1996–2000	43	14.7	63,390	6.5
2001–2005	58	19.8	180,533	9.9
2006–2010	91	31.1	227,647	12.1
2011–2013	67	22.9	1,298,449	69.2

[a] These were studies of patients with mixed diagnoses admitted to a hospital or to specific wards or units of a hospital; mixed populations from inpatient settings (e.g., frail elderly patients; veterans); and mixed patient groups from outpatient clinics.
[b] In the other patient groups category, we grouped studies of patients with cirrhosis, Parkinson's disease, rheumatoid arthritis, liver transplantation, spinal cord injury, or hypertension; patients being weaned from prolonged mechanical ventilation; and elderly patients discharged from a rehabilitation ward after orthopedic surgery on a lower limb.

measurement and account, and 217 (74%) on analyses. After summing up the individual items, we found that 90 studies (31%) had a total score of 3 or less, 104 (36%) a score of 3.5–4, and 99 (34%) a score of 4.5–5.

Excess Mortality in Depressed Versus Nondepressed Participants: Unadjusted Relative Risks

Of the included 293 studies, 238 reported unadjusted outcomes. The overall unadjusted relative risk of mortality

in depressed relative to nondepressed participants in these 238 studies was 1.64 (95% CI=1.56–1.72). Heterogeneity was high and significant (I^2=83, 95% CI=80–84). Exclusion of potential outliers (studies reporting a relative risk ≥4 or <0.25) did not reduce heterogeneity and had only a small effect on the overall relative risk (1.58, 95% CI=1.51–1.65). The results of these meta-analyses are summarized in Table 2.

After adjustment for publication bias with Duvall and Tweedie's trim-and-fill procedure, the overall relative risk was reduced to 1.52 (95% CI=1.45–1.59; the number of filled studies was 41). Egger's test also pointed toward significant publication bias (intercept=1.40, 95% CI=1.01–1.81; p<0.001). A funnel plot with the imputed studies is presented in Figure 2.

Excess Mortality of Depression in Patient and Community Samples

We examined the difference in excess mortality between patient and community samples using subgroup analyses. We found some indications that the mortality rates differed among the populations in our meta-analysis (Table 2; p<0.05). A higher mortality level was found especially in patients with chronic obstructive pulmonary disease (COPD). A direct comparison between the studies of COPD patients and other populations resulted in a highly significant difference (p=0.002). When we removed the studies of COPD patients from the analyses, the remaining populations did not differ significantly from each other.

We conducted several additional sensitivity analyses. First, we excluded the community samples from the analyses (these studies covered more than 90% of the total number of participants included in this meta-analysis; the studies on COPD were not included in these analyses either). The remaining subgroups of studies did not differ significantly from each other. In another analysis, we included only the three largest groups of studies (heart disease, cancer, and kidney diseases) and found no indication of a significant difference between these groups.

Other Subgroup Analyses

In another series of subgroup analyses, we examined whether excess mortality was higher in some groups than in others (Table 2). We found no indication that the relative risk differed between studies that used different measures to define depression (depression according to a diagnostic interview or self-report measure); studies in which different outcome statistics were used (relative risk, hazard ratio, odds ratio, or reported numbers of deaths), and studies conducted in different parts of the world (United States, Europe, other Western countries, East Asia, and other countries).

We found that the relative risk was inversely related to the length of follow-up (p<0.001). We conducted a bivariate meta-regression analysis with time to follow-up (as a continuous variable) as predictor and excess mortality as dependent variable. These analyses also indicated that time to follow-up was a significant predictor of excess mortality (slope=−0.015; 95% CI=−0.017 to −0.013; p<0.000).

We also found that the quality of studies was associated with relative risk. Higher risk of bias indicated higher excess mortality of depression. After summing up the individual items to a total risk of bias score (ranging from 1 [lowest] to 5 [highest]), we conducted a subgroup analysis of the studies with the lowest to the highest risk of bias. As can be seen in Table 2, these analyses indicated that the relative risk was higher in studies with a high risk of bias, while studies with a lower risk of bias indicated a lower, although still significantly elevated, relative risk (p=0.04).

Multivariate Meta-Regression Analyses

To examine the difference in excess mortality between the patient and community samples after adjustment for other characteristics, we conducted a multivariate meta-regression analysis. We used the relative risk as the dependent variable and the variables presented in Table 2 as predictors. As shown in Table 3, the higher relative risk in studies of COPD patients remained significant in these analyses. None of the other types of patient or community samples were significant after adjustment for the other characteristics of the studies. We also found that the two other variables that were significant in the subgroup analyses (time to follow-up and risk of bias) remained significant in the multivariate analyses.

We also conducted a (manual) back-step meta-regression analysis, in which we dropped the least significant variable in each step until only significant predictors were retained in the model (Table 3). The results of this parsimonious model indicated that the three variables that were found to be significant in the full multivariate meta-regression analysis (COPD patients, time to follow-up, and risk of bias) remained significant.

Analyses of Adjusted Outcomes

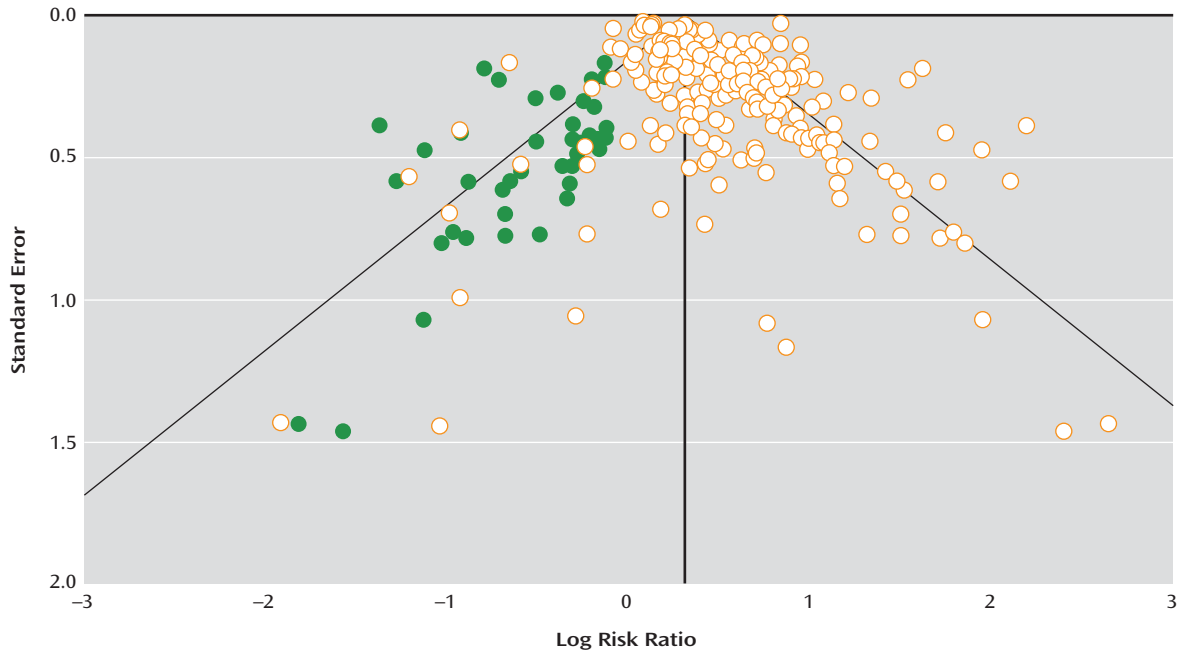
A considerable number of studies reported the association between depression and excess mortality after adjustment for confounders. To pool the results of studies with adjusted outcomes, we grouped the studies reporting adjusted outcomes into four categories in which the relative risk was 1) adjusted for demographic variables; 2) adjusted for lifestyle (at least one lifestyle variable, such as smoking, body mass index, exercise, weight; some studies adjusted simultaneously for one or more demographic variables); 3) adjusted for illness-related variables indicating the severity of a disorder or the presence and severity of comorbid disorders (with or without simultaneous adjustment for demographic variables); and 4) adjusted for lifestyle and illness-related factors. As can be seen in Table 4, the overall relative risk decreased

TABLE 2. Unadjusted Relative Risk of Excess Mortality in Depressed Compared With Nondepressed Participants[a]

Analysis and Measure	N	Relative Risk	95% CI	Heterogeneity[b] I^2	Heterogeneity[b] 95% CI	Heterogeneity[b] p
Unadjusted analyses						
All studies	238	1.64	1.56–1.72	83***	80–84	
18 outliers excluded[c]	220	1.58	1.51–1.65	82***	79–84	
Adjusted for publication bias (number of filled studies, 41)		1.52	1.45–1.59			
Outcomes for specific groups						0.047
Community samples	78	1.59	1.47–1.71	90***	89–92	
Heart disease patients	65	1.72	1.56–1.90	73***	66–79	
Cancer patients	23	1.61	1.37–1.88	50**	19–69	
Kidney disease patients	14	1.66	1.35–2.03	36	0–66	
Chronic obstructive pulmonary disease patients	7	2.72	1.96–3.77	81***	63–91	
Diabetes patients	6	1.61	1.21–2.15	25	0–69	
Stroke patients	5	1.26	0.92–1.72	66*	10–87	
Mixed patient groups	17	1.51	1.25–1.82	70***	52–82	
Other patient groups[d]	9	1.69	1.26–2.28	55*	6–79	
Nursing home residents	9	1.61	1.27–2.03	32	0–69	
Case-control studies	5	2.51	1.65–3.81	0	0–79	
Other subgroup analyses						
Definition of depression						0.97
Diagnostic interview	72	1.64	1.49–1.80	67***	57–74	
Self-report measure	166	1.64	1.56–1.73	85***	84–87	
Prevalence of depression						0.38
<10%	33	1.77	1.56–2.01	75***	66–82	
10%–19%	60	1.65	1.51–1.80	90***	87–92	
20%–29%	58	1.58	1.44–1.73	78***	72–83	
30%–40%	32	1.80	1.57–2.06	73***	61–81	
>40%	38	1.56	1.38–1.76	72***	62–80	
Not reported	17	1.51	1.26–1.81	37	0–65	
Follow-up period[e]						<0.01
≤1 year	51	1.83	1.63–2.06	33*	5–53	
1–2 years	38	1.79	1.58–2.02	62***	47–74	
3–5 years	64	1.73	1.59–1.88	73***	65–79	
5–10 years	59	1.61	1.49–1.74	88***	86–90	
>10 years	24	1.29	1.15–1.44	86***	80–90	
Outcome statistic						0.74
Hazard ratio	68	1.69	1.56–1.84	78***	72–82	
Relative risk based on numbers	152	1.61	1.52–1.70	78***	75–81	
Relative risk (given in study)	11	1.59	1.30–1.96	79***	63–88	
Odds ratio	7	1.59	1.20–2.11	44	0–77	
Country						0.08
United States	90	1.58	1.47–1.70	74***	68–79	
European countries	92	1.74	1.62–1.87	84***	81–87	
Other Western countries	25	1.42	1.24–1.63	85***	79–89	
East Asian countries	19	1.72	1.46–2.04	73***	58–83	
Other countries	12	1.76	1.34–2.30	43	0–71	
Risk of bias						0.04
1 (highest)	8	2.44	1.81–3.28	0	0–68	
2	31	1.72	1.48–2.00	67***	52–77	
3	38	1.77	1.55–2.01	79***	72–84	
4	84	1.61	1.48–1.74	88***	86–90	
5 (lowest)	77	1.57	1.45–1.70	80***	75–83	

[a] Hazard ratios and odds ratios were treated as if they were relative risks.
[b] The p value here indicates whether the Q statistic was significant.
[c] Studies with a relative risk ≥4 or <0.25 were considered to be outliers.
[d] In the other patient groups category, we grouped the following studies together: patients with cirrhosis, dementia, hip fracture/surgery, HIV, liver transplantation, Parkinson's disease; patients being weaned from prolonged mechanical ventilation; and elderly patients discharged from a rehabilitation ward after orthopedic surgery on a lower limb.
[e] Three studies for which the follow-up period was not clear were excluded from these analyses.
* p<0.05. **p<0.01. ***p<0.001.

FIGURE 2. Funnel Plot of Standard Error by Log Relative Risk of Excess Mortality in Adult Depression: Actual and Imputed Studies[a]



[a] The white circles indicate actual studies, and the green circles indicate the imputed studies—those that would have been there if the funnel plot had been symmetrical. The vertical line represents the pooled log relative risk after adjustment for publication bias. The diagonal lines represent the borders of the funnel plot.

somewhat after adjustment for these variables, with a lower relative risk when more categories of variables were entered into the models.

There were few indications of significant differences between community and patient samples for adjusted mortality risks. There was, however, a significant difference between subgroups in the studies in which the results were adjusted for illness-related factors ($p<0.05$). In studies of heart disease patients especially, the relative risk was higher than in other populations.

Because of the considerable differences between the variables for which the outcomes were adjusted in individual studies, the relatively small number of studies in each of the four categories, and the high level of heterogeneity of the pooled outcomes, we did not conduct any additional analyses with these samples.

Discussion

In this meta-analysis we did not find strong indications that excess mortality associated with depression is significantly higher in one or more patient groups or in community-based samples, except for a significantly higher risk in studies of COPD patients. Our observation that the association between depression and mortality is not strikingly different between community-based samples and patient samples suggests that the association between depression and mortality may be explained better by generic mechanisms, such as biological dysregulations and lifestyle factors that have a general impact on health, than by disorder-specific mechanisms, such as vascular endothelial dysfunction, stimulated tumor growth, or increased platelet aggregation.

It is not clear why the studies of COPD patients resulted in a higher risk of mortality than those of other (patient and community-based) samples. It is possible that this is a chance finding, because the number of studies was relatively low (N=7). However, it is also possible that this finding is related to COPD-related variables, such as airflow limitation, hypercapnia, hypoxemia, increased dyspnea, and poor nutritional status, all of which have been found to be risk factors for mortality in COPD patients (24), which in turn may somehow be related to depression.

The fact that for most categories of studies no significant differences were found in mortality rates according to depression status should be considered with caution. The specific patient groups may not be as distinct as they appear, as these patients may very well have suffered from all kinds of comorbidities. Quite a few patients with cancer also have heart disease, and many patients with diabetes also have renal disease. Thus, deaths occurring in these populations may not be related to the disease being studied but to a comorbid disease. For example, cardiac death is common among diabetes patients. In addition, even when mortality rates are comparable in different populations, that does not automatically mean that the mechanisms leading to death are the same in the different

TABLE 3. Multivariate Meta-Regression Analyses of Study Characteristics and Effect Sizes

	Full Model			Parsimonious Model[a]		
	Coefficient	SE	p	Coefficient	SE	p
Group						
Heart disease patients	Reference					
Cancer patients	–0.07	0.10	0.50			
Kidney disease patients	–0.12	0.12	0.33			
Chronic obstructive pulmonary disease patients	0.39	0.19	0.04	0.48	0.18	0.008
Other patient groups	–0.09	0.08	0.23			
Other populations	0.14	0.15	0.35			
Community samples	–0.05	0.07	0.50			
Diagnostic interview (versus self-report measure)	–0.07	0.06	0.25			
Prevalence of depression[b]	–0.002	0.002	0.21			
Follow-up period[b]	–0.02	0.004	<0.001	–0.01	0.004	<0.001
Outcome statistic						
Hazard ratio	Reference					
Relative risk based on numbers	–0.12	0.06	0.05			
Relative risk (given in study)	0.06	0.13	0.65			
Odds ratio	–0.18	0.16	0.27			
Country						
United States	Reference					
European countries	0.05	0.06	0.44			
Other Western countries	–0.09	0.08	0.27			
East Asian countries	0.05	0.10	0.63			
Other countries	0.07	0.14	0.61			
Risk of bias[b]	–0.07	0.03	0.01	–0.07	0.02	0.005
Publication year[b]	<–0.001	0.004	0.88			
Constant	2.41	8.78	0.78	0.83	0.10	<0.001

[a] In the parsimonious model, the least significant variable was dropped in each step of a backward regression analysis, until only significant predictors ($p<0.05$) were retained.
[b] Entered in the model as continuous variables.

populations. For example, nonadherence to medication use may be life-threatening in one population but not in another, and elevations of a particular inflammatory marker may have different implications for a cancer patient than for a patient with heart disease.

We also found in our meta-analysis that heterogeneity of the pooled relative risk was considerable. This suggests that other factors that we did not examine in this meta-analysis had a considerable influence on the outcomes, and we cannot rule out the possibility that some of these factors are disease specific. It is also possible that the heterogeneity may be explained in part by depression-related variables that we did not measure, such as severity, number of depressive episodes, and duration of illness. However, in this context it is remarkable that we did not find any significant differences in the excess mortality rates for psychiatric diagnoses of depression, which are generally more severe, than for self-reported symptoms of depression, which often indicate subthreshold depression (25). Therefore, more research is needed to establish the exact mechanisms connecting depression and excess mortality.

This meta-analysis confirmed that there is a highly significant association between depression and excess mortality at follow-up. However, we found indications that this association may have been overestimated in earlier research because of publication bias and because of a stronger association between depression and excess mortality in studies of lower quality. Despite the likely overestimation, the association remains highly significant, even after adjustment for publication bias and low quality.

This study showed once again that depression is an important clinical and public health problem. Because of the high prevalence of depression, the associated excess mortality may have a high impact on public health. An earlier study (25) found, for example, that the population attributable fraction of major depression was 10%, indicating that mortality rates would go down 10% if depression could be eliminated completely. For clinicians, it is also important to realize that depression is associated with excess mortality, and the assessment of physical health in depressed patients is always important.

Prevalence rates of depression may vary, with higher rates in patient groups than in community samples. When the prevalence of depression is higher, the public health impact on mortality is also higher (i.e., higher population

TABLE 4. Adjusted Relative Risk of Excess Mortality in Depressed Compared With Nondepressed Participants[a]

Adjustment and Group	N	Relative Risk	95% CI	Heterogeneity[b] I^2	Heterogeneity[b] 95% CI	p[c]
Demographic variables						
All studies	22	1.66	1.53–1.79	66***	51–77	0.63
Community samples	18	1.68	1.52–1.86	70***	51–81	
Other somatic illness samples	15	1.62	1.42–1.84	63	36–79	
Lifestyle factors, all studies[d]	11	1.54	1.35–1.75	78***	61–88	
Illness-related factors[e]						
All studies	77	1.54	1.42–1.68	75***	69–80	0.03
Community samples	19	1.33	1.15–1.53	79***	67–86	
Heart disease samples	18	1.90	1.59–2.30	49**	13–71	
Cancer samples	9	1.53	1.15–2.05	81***	64–90	
Other	31	1.56	1.36–1.78	72***	61–81	
Lifestyle and illness-related factors						
All studies	58	1.45	1.35–1.55	77***	70–82	0.37
Community samples	28	1.42	1.30–1.55	83***	77–88	
Heart disease samples	11	1.36	1.14–1.62	45*	0–73	
Other somatic illness samples	13	1.56	1.37–1.78	63***	39–77	

[a] When there were five or fewer studies in one subgroup these were clustered together in the category "other somatic illness."
[b] The asterisks in the I^2 column indicate the significance level of the Q statistic.
[c] This p value indicates whether the effect sizes in the subgroups differ significantly from each other.
[d] Only two of the 11 studies were patient samples; we considered this subgroup too small to conduct subgroup analyses. Lifestyle factors include variables such as smoking, body mass index, exercise, and alcohol use.
[e] Illness-related factors include illness-related variables indicating the severity of a disorder and the presence and severity of comorbid disorders.
* $p<0.05$. ** $p<0.01$. *** $p<0.001$.

attributable risk), although the relative risk is the same in higher- and lower-prevalence populations.

This study has several strengths and limitations. The major strength is its broad scope and the large number of included studies and participants, which allowed us to directly examine whether excess mortality is comparable across different populations. At the same time, however, this is also one of the limitations of the study. Such a broad scope inevitably results in high levels of heterogeneity, and we were unable to identify the causes that can fully explain this heterogeneity. Another limitation is that the quality of many of the included studies was not optimal, and this may have affected our outcomes, especially since we found a significant association between study quality and outcome.

Despite these limitations, however, this study has once again confirmed a significant association between depression and excess mortality at follow-up. This excess mortality is comparable in community samples and most patient populations, and although the evidence is not conclusive, this suggests that generic and not disease-specific mechanisms may be the most likely mechanisms for the excess mortality among depressed persons.

Received March 19, 2013; revision received Oct. 12, 2013; accepted Nov. 18, 2013 (doi: 10.1176/appi.ajp.2013.13030325). From the Department of Clinical Psychology, VU University Amsterdam, the Netherlands; the Department of Psychiatry, VU University Medical Center, Amsterdam; the EMGO Institute for Health and Care Research, Amsterdam; and the Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing. Address correspondence to Dr. Cuijpers (p.cuijpers@vu.nl).

The authors report no financial relationships with commercial interests.

References

1. Odegard O: Excess mortality of the insane. Acta Psychiatr Scand 1952; 27:353–367
2. Alström CH: Mortality in mental hospitals. Acta Psychiatr Neurol Scand Suppl 1942; 24:1–415
3. Cuijpers P, Smit F: Excess mortality in depression: a meta-analysis of community studies. J Affect Disord 2002; 72:227–236
4. Barth J, Schumacher M, Herrmann-Lingen C: Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. Psychosom Med 2004; 66:802–813
5. Chida Y, Hamer M, Wardle J, Steptoe A: Do stress-related psychosocial factors contribute to cancer incidence and survival? Nat Clin Pract Oncol 2008; 5:466–475
6. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB: Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. JAMA 2011; 306:1241–1249
7. Lin EHB, Heckbert SR, Rutter CM, Katon WJ, Ciechanowski P, Ludman EJ, Oliver M, Young BA, McCulloch DK, Von Korff M: Depression and increased mortality in diabetes: unexpected causes of death. Ann Fam Med 2009; 7:414–421
8. Kiecolt-Glaser JK, Stephens RE, Lipetz PD, Speicher CE, Glaser R: Distress and DNA repair in human lymphocytes. J Behav Med 1985; 8:311–320
9. Yang EV, Glaser R: Stress-induced immunomodulation: implications for tumorigenesis. Brain Behav Immun 2003; 17(suppl 1): S37–S40
10. Seruga B, Zhang H, Bernstein LJ, Tannock IF: Cytokines and their relationship to the symptoms and outcome of cancer. Nat Rev Cancer 2008; 8:887–899

11. Stapelberg NJ, Neumann DL, Shum DH, McConnell H, Hamilton-Craig I: A topographical map of the causal network of mechanisms underlying the relationship between major depressive disorder and coronary heart disease. Aust N Z J Psychiatry 2011; 45:351–369
12. Whang W, Julien HM, Higginbotham L, Soto AV, Broodie N, Bigger JT, Garan H, Burg MM, Davidson KW: Women, but not men, have prolonged QT interval if depressed after an acute coronary syndrome. Europace 2012; 14:267–271
13. Carney RM, Freedland KE, Miller GE, Jaffe AS: Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. J Psychosom Res 2002; 53:897–902
14. Cuijpers P, Schoevers RA: Increased mortality in depressive disorders: a review. Curr Psychiatry Rep 2004; 6:430–437
15. Vreeburg SA, Hoogendijk WJ, van Pelt J, Derijk RH, Verhagen JC, van Dyck R, Smit JH, Zitman FG, Penninx BW: Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. Arch Gen Psychiatry 2009; 66:617–626
16. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL: A meta-analysis of cytokines in major depression. Biol Psychiatry 2010; 67:446–457
17. Hayden JA, Côté P, Bombardier C: Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med 2006; 144:427–437
18. Landis JR, Koch GG: The measurement of observer agreement for categorical data. Biometrics 1977; 33:159–174
19. Higgins JP, Thompson SG, Deeks JJ, Altman DG: Measuring inconsistency in meta-analyses. BMJ 2003; 327:557–560
20. Ioannidis JPA, Patsopoulos NA, Evangelou E: Uncertainty in heterogeneity estimates in meta-analyses. BMJ 2007; 335: 914–916
21. Orsini N, Bottai M, Higgins J, Buchan I: Heterogi: Stata module to quantify heterogeneity in a meta-analysis (software program) (Statistical Software Components S449201). Boston, Boston College, Department of Economics, 2005
22. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR: Introduction to Meta-Analysis. Chichester, UK, Wiley, 2009
23. Duval S, Tweedie R: Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000; 56:455–463
24. de Voogd JN, Wempe JB, Koëter GH, Postema K, van Sonderen E, Ranchor AV, Coyne JC, Sanderman R: Depressive symptoms as predictors of mortality in patients with COPD. Chest 2009; 135: 619–625
25. Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx BW: Differential mortality rates in major and subthreshold depression: meta-analysis of studies that measured both. Br J Psychiatry 2013; 202:22–27